

Claims

1. An isolated antibody, or antigen binding portion thereof, that binds to human Cluster of Differentiation 73 (CD73), and comprises a heavy chain comprising CDR1, CDR2, and CDR3 sequences comprising the amino acid sequences of SEQ ID NOs: 5, 6, and 7, respectively, and a light chain comprising CDR1, CDR2, and CDR3 sequences comprising the amino acid sequences of SEQ ID NOs: 13, 14, and 15, respectively.
2. An isolated antibody that binds to human CD73 and comprises a heavy chain comprising CDR1, CDR2, and CDR3 sequences comprising the amino acid sequences of SEQ ID NOs: 5, 6, and 7, respectively, and a light chain comprising CDR1, CDR2, and CDR3 sequences comprising the amino acid sequences of SEQ ID NOs: 13, 14, and 15, respectively.
3. The isolated antibody, or antigen binding portion thereof, of claim 1 or the isolated antibody of claim 2, comprising heavy and light chain variable regions, wherein the heavy and light chain variable regions comprise the amino acid sequences of SEQ ID NOs: 135 and 12, respectively.
4. The isolated antibody, or antigen binding portion thereof, of any one of claims 1 to 3, which binds to human CD73 with a K_D of 0.1 nM to 10 nM, as determined by Surface Plasmon Resonance (SPR).
5. The isolated antibody, or antigen binding portion thereof, of any one of claims 1 to 3,, which inhibits the activity of human CD73.
6. The isolated antibody, or antigen binding portion thereof, of any one of claims 1 to 3,, which mediates internalization of human CD73.
7. The isolated antibody, or antigen binding portion thereof, of any one of claims 1 to 3,, which has reduced effector function relative to a wild type IgG1 antibody.
8. The isolated antibody, or antigen binding portion thereof, of claim 1, which is a human IgG antibody.
9. The isolated antibody, or antigen binding portion thereof, of claim 1, which is a human IgG1, IgG2, or IgG4 antibody.

10. The isolated antibody, or antigen binding portion thereof, of claim 1, comprising a heavy chain sequence comprising the amino acid sequence of SEQ ID NO: 133 or 189 and a light chain sequence comprising the amino acid sequence of SEQ ID NO: 102.
11. The isolated antibody, or antigen binding portion thereof, of claim 10, comprising a heavy chain consisting of the amino acid sequence of SEQ ID NO: 133 and a light chain consisting of the amino acid sequence of SEQ ID NO: 102.
12. The isolated antibody, or antigen binding portion thereof, of claim 10, comprising a heavy chain consisting of the amino acid sequence of SEQ ID NO: 189 and a light chain consisting of the amino acid sequence of SEQ ID NO: 102.
13. The isolated antibody, or antigen binding portion thereof, of claim 1, comprising two heavy chains and two light chains, wherein each of the heavy chains consists of the amino acid sequence of SEQ ID NO: 133 or 189 and each of the light chains consists of the amino acid sequence of SEQ ID NO: 102.
14. The isolated antibody, or antigen binding portion thereof, of claim 13, further comprising intermolecular disulfide bonding between the two heavy chain constant regions.
15. A composition comprising the antibody, or antigen binding portion thereof, of any one of claims 1 to 3, and a pharmaceutically acceptable carrier.
16. The composition of claim 15, further comprising one or more additional therapeutic agents.
17. The composition of claim 16, wherein the additional therapeutic agent is a programmed cell death protein 1 (PD-1) antagonist, a programmed death-ligand 1 (PD-L1) antagonist, a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antagonist, and/or a lymphocyte activation gene-3 (LAG-3) antagonist.
18. A composition comprising the antibody, or antigen binding portion thereof, of any one of claims 10 to 12, and a pharmaceutically acceptable carrier.
19. The composition of claim 18, further comprising one or more additional therapeutic agents.

20. The composition of claim 19, wherein the additional therapeutic agent is a programmed cell death protein 1 (PD-1) antagonist, a programmed death-ligand 1 (PD-L1) antagonist, a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antagonist, and/or a lymphocyte activation gene-3 (LAG-3) antagonist.
21. An isolated antibody, or antigen binding portion thereof, which comprises heavy and light chain variable regions, wherein the heavy and light chain variable regions comprise the amino acid sequences of SEQ ID NOs: 135 and 12, respectively.
22. The isolated antibody, or antigen binding portion thereof, of claim 21, comprising heavy and light chain variable regions, wherein the heavy and light chain variable regions consist of the amino acid sequences of SEQ ID NOs: 135 and 12, respectively.
23. The isolated antibody, or antigen binding portion thereof, of claim 21, comprising a heavy chain sequence comprising the amino acid sequence of SEQ ID NO: 133 or 189 and a light chain sequence comprising the amino acid sequence of SEQ ID NO: 102.
24. The isolated antibody, or antigen binding portion thereof, of claim 21 comprising two heavy chains and two light chains, wherein each of the heavy chains consists of the amino acid sequence of SEQ ID NO: 133 or 189 and each of the light chains consists of the amino acid sequence of SEQ ID NO: 102.
25. The isolated antibody, or antigen binding portion thereof, of claim 24, further comprising intermolecular disulfide bonding between the two heavy chain constant regions.
26. A composition comprising the antibody, or antigen binding portion thereof, of any one of claims 21 or 23, and a pharmaceutically acceptable carrier.
27. The composition of claim 26, further comprising one or more additional therapeutic agents.
28. The composition of claim 27, wherein the additional therapeutic agent is a programmed cell death protein 1 (PD-1) antagonist, a programmed death-ligand 1 (PD-L1) antagonist, a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antagonist, and/or a lymphocyte activation gene-3 (LAG-3) antagonist.

29. An isolated antibody that binds to human CD73 and comprises a heavy chain comprising CDR1, CDR2, and CDR3 sequences comprising the amino acid sequences of SEQ ID NOs: 5, 6, and 7, respectively, and a light chain comprising CDR1, CDR2, and CDR3 sequences comprising the amino acid sequences of SEQ ID NOs: 13, 14, and 15, respectively, wherein the heavy chain is a full-length heavy chain and the light chain is a full-length light chain.

30. An isolated antibody that binds to human CD73 and comprises heavy and light chain variable regions, wherein the heavy and light chain variable regions comprise the amino acid sequences of SEQ ID NOs: 135 and 12, respectively, wherein the heavy chain is a full-length heavy chain and the light chain is a full-length light chain.

31. The isolated antibody of any one of claims 29 or 30, which is an IgG antibody.

32. An isolated nucleic acid molecule encoding the heavy and light chains of the isolated antibody of claims 2 or 3.

33. An isolated nucleic acid molecule encoding the heavy and light chains of the isolated antibody of claims 11 or 12

34. The isolated nucleic acid molecule of claim 32 wherein the heavy chain is a full length heavy chain and the light chain is a full length light chain.

35. The isolated nucleic acid molecule of claim 32 wherein the isolated antibody is an IgG antibody.

36. The isolated nucleic acid molecule of claim 35 wherein the isolated antibody comprises an IgG2 hinge.

37. The isolated nucleic acid molecule of claim 32 wherein the isolated antibody (a) binds to human CD73 with a $K_{sub.D}$ of 0.1 nM to 10 nM, as determined by Surface Plasmon Resonance (SPR); (b) inhibits the activity of human CD73; or (c) mediates internalization of human CD73.

38. An expression vector comprising the isolated nucleic acid molecule of any one of claims 32 or 33.

39. An isolated cell transformed with the expression vector of claim 38.
40. The isolated antibody, or antigen binding portion thereof, of claim 1 or the isolated antibody of claim 2 for use in therapy.
41. The isolated antibody, or antigen binding portion thereof, of claim 1 or the isolated antibody of claim 2 for use as a medicament.
42. The isolated antibody, or antigen binding portion thereof, of claim 1 or the isolated antibody of claim 2 for use in decreasing adenosine levels in a tumor of a human subject.
43. The isolated antibody, or antigen binding portion thereof, of claim 1 or the isolated antibody of claim 2 for use in stimulating an immune response against a tumor in a human subject in need thereof.
44. The isolated antibody, or antigen binding portion thereof, of claim 1 or the isolated antibody of claim 2 for use in stimulating an immune response in a human subject.
45. The isolated antibody, or antigen binding portion thereof, of claim 1 or the isolated antibody of claim 2 for use in inhibiting the growth of a tumor in a human subject.
46. The isolated antibody, or antigen binding portion thereof, of claim 1 or the isolated antibody of claim 2 for use in treating cancer in a human subject.
47. The isolated antibody, or antigen binding portion thereof or the isolated antibody for use according to claim 46, wherein the cancer is selected from the group consisting of: bladder cancer, breast cancer, uterine/cervical cancer, ovarian cancer, prostate cancer, testicular cancer, esophageal cancer, gastrointestinal cancer, pancreatic cancer, colorectal cancer, colon cancer, kidney cancer, head and neck cancer, lung cancer, stomach cancer, germ cell cancer, bone cancer, liver cancer, thyroid cancer, skin cancer, neoplasm of the central nervous system, lymphoma, leukemia, myeloma, sarcoma, and virus-related cancer.
48. The isolated antibody, or antigen binding portion thereof or the isolated antibody for use according to claim 46, wherein one or more additional therapeutic agents is to be administered to the human subject.

49. The isolated antibody, or antigen binding portion thereof or the isolated antibody for use according to claim 48, wherein the additional therapeutic agents is a PD-1 antagonist, a PD-L1 antagonist, a CTLA-4 antagonist, or a LAG-3 antagonist.

50. The isolated antibody, or antigen binding portion thereof or the isolated antibody for use according to claim 46, wherein the isolated antibody, or antigen binding portion thereof or the isolated antibody comprises heavy and light chain variable regions comprising the amino acid sequences of SEQ ID NOs: 135 and 12, respectively.

51. The isolated antibody, or antigen binding portion thereof or the isolated antibody for use according to claim 46, wherein the isolated antibody, or antigen binding portion thereof or the isolated antibody comprises a heavy chain sequence comprising the amino acid sequence of SEQ ID NO: 133 or 189 and a light chain sequence comprising the amino acid sequence of SEQ ID NO: 102.

52. The isolated antibody, or antigen binding portion thereof or the isolated antibody for use according to claim 46, wherein the heavy chain is a full-length heavy chain and the light chain is a full-length light chain.

53. The isolated antibody, or antigen binding portion thereof or the isolated antibody for use according to claim 50, wherein the heavy chain is a full-length heavy chain and the light chain is a full-length light chain.

54. The isolated antibody, or antigen binding portion thereof or the isolated antibody for use according to claim 46, wherein the isolated antibody, or antigen binding portion thereof or the isolated antibody is an IgG antibody.

55. The isolated antibody, or antigen binding portion thereof or the isolated antibody for use according to claim 51 wherein the isolated antibody, or antigen binding portion thereof or the isolated antibody comprises a heavy chain consisting of the amino acid sequence of SEQ ID NO: 133 and a light chain consisting of the amino acid sequence of SEQ ID NO: 102.

56. The isolated antibody, or antigen binding portion thereof or the isolated antibody for use according to claim 51 wherein the isolated antibody, or antigen binding portion thereof or the isolated antibody comprises a heavy chain consisting of the amino acid sequence of SEQ ID NO: 189 and a light chain consisting of the amino acid sequence of SEQ ID NO: 102.

57. The isolated antibody, or antigen binding portion thereof or the isolated antibody for use according to claim 46, wherein the isolated antibody, or antigen binding portion thereof or the isolated antibody binds to human CD73 with a K_D of 0.1 nM to 10 nM, as determined by Surface Plasmon Resonance (SPR).

58. The isolated antibody, or antigen binding portion thereof or the isolated antibody for use according to claim 46, wherein the isolated antibody, or antigen binding portion thereof or the isolated antibody inhibits the activity of human CD73.

59. The isolated antibody, or antigen binding portion thereof or the isolated antibody for use according to claim 46, wherein the isolated antibody, or antigen binding portion thereof or the isolated antibody mediates internalisation of human CD73.

60. The isolated antibody, or antigen binding portion thereof or the isolated antibody for use according to claim 46, wherein the isolated antibody, or antigen binding portion thereof or the isolated antibody has reduced effector function relative to a wild type IgG1 antibody.

61. The isolated antibody, or antigen binding portion thereof or the isolated antibody for use according to claim 46, wherein the isolated antibody, or antigen binding portion thereof or the isolated antibody binds to human CD73 with a K_D of 0.1 nM to 10 nM, as determined by Surface Plasmon Resonance (SPR).

62. The use of the isolated antibody, or antigen binding portion thereof, of claim 1 or the isolated antibody of claim 2 in the manufacture of a medicament for decreasing adenosine levels in a tumor of a human subject.

63. The use of the isolated antibody, or antigen binding portion thereof, of claim 1 or the isolated antibody of claim 2 in the manufacture of a medicament for stimulating an immune response against a tumor in a human subject in need thereof.

64. The use of the isolated antibody, or antigen binding portion thereof, of claim 1 or the isolated antibody of claim 2 in the manufacture of a medicament for stimulating an immune response in a human subject.

65. The use of the isolated antibody, or antigen binding portion thereof, of claim 1 or the isolated antibody of claim 2 in the manufacture of a medicament for inhibiting the growth of a tumor in a human subject.

66. The use of the isolated antibody, or antigen binding portion thereof, of claim 1 or the isolated antibody of claim 2 in the manufacture of a medicament for treating cancer in a human subject.

67. The use according to claim 66, wherein the cancer is selected from the group consisting of: bladder cancer, breast cancer, uterine/cervical cancer, ovarian cancer, prostate cancer, testicular cancer, esophageal cancer, gastrointestinal cancer, pancreatic cancer, colorectal cancer, colon cancer, kidney cancer, head and neck cancer, lung cancer, stomach cancer, germ cell cancer, bone cancer, liver cancer, thyroid cancer, skin cancer, neoplasm of the central nervous system, lymphoma, leukemia, myeloma, sarcoma, and virus-related cancer.

68. The use according to claim 66, wherein one or more additional therapeutic agents is to be administered to the human subject.

69. The use according to claim 68, wherein the additional therapeutic agents is a PD-1 antagonist, a PD-L1 antagonist, a CTLA-4 antagonist, or a LAG-3 antagonist.

70. The use according to claim 66, wherein the medicament comprises heavy and light chain variable regions comprising the amino acid sequences of SEQ ID NOs: 135 and 12, respectively.

71. The use according to claim 66, wherein the medicament comprises a heavy chain sequence comprising the amino acid sequence of SEQ ID NO: 133 or 189 and a light chain sequence comprising the amino acid sequence of SEQ ID NO: 102.

72. The use according to claim 66, wherein the heavy chain is a full-length heavy chain and the light chain is a full-length light chain.

73. The use according to claim 70, wherein the heavy chain is a full-length heavy chain and the light chain is a full-length light chain.

74. The use according to claim 66, wherein the isolated antibody, or antigen binding portion thereof or the isolated antibody is an IgG antibody.

75. The use according to claim 71 wherein the medicament comprises a heavy chain consisting of the amino acid sequence of SEQ ID NO: 133 and a light chain consisting of the amino acid sequence of SEQ ID NO: 102.

76. The use according to claim 71 wherein the medicament comprises a heavy chain consisting of the amino acid sequence of SEQ ID NO: 189 and a light chain consisting of the amino acid sequence of SEQ ID NO: 102.

77. The use according to claim 66, wherein the isolated antibody, or antigen binding portion thereof or the isolated antibody binds to human CD73 with a K_D of 0.1 nM to 10 nM, as determined by Surface Plasmon Resonance (SPR).

78. The use according to claim 66, wherein the medicament inhibits the activity of human CD73.

79. The use according to claim 66, wherein the medicament mediates internalisation of human CD73.

80. The isolated antibody, or antigen binding portion thereof or the isolated antibody for use according to claim 66, wherein the medicament has reduced effector function relative to a wild type IgG1 antibody.

81. The isolated antibody, or antigen binding portion thereof or the isolated antibody for use according to claim 66, wherein the isolated antibody, or antigen binding portion thereof or the isolated antibody binds to human CD73 with a K_D of 0.1 nM to 10 nM, as determined by Surface Plasmon Resonance (SPR).